Insulin-Like Growth Factor Receptor

George Blumenschein, Jr, MD

The insulin-like growth factor (IGF) signaling axis plays an essential role in the balance between cellular proliferation and apoptosis. Higher levels of IGF receptor are seen in lung tumor cells than normal tissue. IGF-1 receptor (IGFR-1R) and its ligand IGF-2 is overexpressed in non-small cell lung cancer (NSCLC). Elevated levels of IGF-1 in plasma are associated with an increased risk of developing lung cancer, and IGF-1R has been shown to promote the proliferation of lung cancer cells in vitro.[1] IGF-1R can hybridize with other membrane receptors leading to the activation of different tyrosine kinase domains.[2] The central role that the IGFR pathway plays in various signaling pathways in tumor cells makes the IGF axis an attractive target for therapeutic intervention.

Dr. Pollak presented an overview of the science of the IGFR to establish the rationale for the development of this class of drugs for the treatment of NSCLC. There are a number of possible avenues through which the effects of IGF can be inhibited. These strategies include antibodies directed against IGF ligand, IGF-1R tyrosine kinase inhibitors, and antibodies targeting the IGF-1R. The approach of blocking the IGF-1 receptor tyrosine kinase pathway and the insulin receptor (IR) via signal transduction inhibitors is also undergoing clinical evaluation.

IMC-A12

IMC-A12 is a fully humanized IgG1 monoclonal antibody with a half-life of 15 to 21 days that targets the IGF-1 receptor.[3] Both weekly and q21-day schedules are being explored. There are three ongoing randomized phase II trials with different first-line platinum-based regimens including a trial that is comparing gemcitabine, carbopatin with the addition of IMC-A12, cetuximab, or both, and another evaluating carboplatin, paclitaxel bevacizumab with or without IMC-A12 in nonsquamous NSCLC. There is one randomized first-line trial of etoposide, cisplatin with or without either IMC-A12 or the hedgehog inhibitor GDC-0449 in extensive disease small cell lung cancer (EDSCLC). The combination of erlotinib plus A12 was closed due to toxicity of the combination. Currently, no additional toxicity or efficacy data are available.

Department of Thoracic and Head and Neck Medical Oncology, The University of Texas, MD Anderson Cancer Center, Houston, Texas.
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Address for correspondence: George R. Blumenschein, Jr, MD, Associate Professor of Medicine, Department of Thoracic and Head and Neck Medical Oncology, The University of Texas, MD Anderson Cancer Center, 1515 Holcombe Blvd, Unit 432, Houston, TX 77030. E-mail: gblumens@mdanderson.org

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AMG-479

Phase I studies established thrombocytopenia as the dose-limiting toxicity of AMG-479, a fully human monoclonal antibody to IGF-1R.[4] AMG-479 is being evaluated in the front-line setting in combination with etoposide and carboplatin or cisplatin in a randomized phase I/II trial in patients with EDSCLC. Patients will receive up to six cycles of the combination then single-agent AMG 479 as maintenance therapy until disease progression. Preliminary results indicate that AMG-479 can be safely combined with etoposide and cisplatin (or carboplatin) in this patient population without impact on the delivery of AMG-479 or the chemotherapy. Activity in the phase I portion was similar to reported with chemotherapy alone.[5] The phase II portion of the trial has completed accrual and results are pending.

MK-0646

MK-0646 is a fully humanized monoclonal IgG1 antibody that selectively binds to the IGF-1 receptor and not to the insulin receptor.[6] The recommended phase II dose is 10 mg/kg weekly. An overview of the compound and the design of several clinical trials were presented. In the randomized phase II IMPACT study, MK-0646 is being evaluated in combination with pemetrexed (500 mg/m^2) and cisplatin (75 mg/m^2) as first-line therapy in patients with stage IIIB or IV nonsquamous NSCLC. The phase I/II design of MK-0646 plus cisplatin and etoposide in patients with treatment-naive EDSCLC was also presented. Both studies are ongoing but not actively recruiting participants.

OSI-906

Phase I studies of OSI-906, an oral tyrosine kinase inhibitor of IGF-1R and IR established a continuous daily dosing (150 mg twice daily or 400 mg daily) and an intermittent schedule (600 mg 1 week on/1 week off as part of a 2-week cycle) for further exploration in the phase II setting.

Subsequently, a phase I clinical trial combining OSI-906 with erlotinib for patients with refractory NSCLC was completed. This trial established OSI-906 150 mg BID with erlotinib at 150 mg daily as the phase II dose. Two patients with NSCLC had partial responses on this regimen. The common adverse events reported included rash, hyperglycemia, diarrhea, and fatigue.[7] This combination of OSI-906 plus erlotinib is being evaluated in ongoing randomized phase II trials including a front-line therapy trial for patients with EGFR mutation positive metastatic NSCLC who receive erlotinib with or without the addition of OSI-906. A second trial explores the role of OSI-906 as maintenance therapy in patients with metastatic NSCLC who do not have progression of disease after completing four cycles of first-line platinum-based chemotherapy and are then randomized to either erlotinib or erlotinib plus OSI-906.

BMS-754807

BMS-754807, a oral dual kinase reversible inhibitor of IR and IGF-1R. Preliminary phase I results indicate that the drug is well tolerated as a single agent with common adverse events including diarrhea, constipation, nausea, vomiting, and fatigue.[8] The ongoing phase I combination trial has demonstrated that BMS-745807 can be safely administered with carboplatin and paclitaxel with no reported DLTs to date.[9] Additional clinical trials with BMS-754807 as a single agent or in combination with various agents (cetuximab, herceptin, carboplatin, and paclitaxel) in solid tumors are underway.

Future Directions

There are a number of agents targeting the IGF signaling pathway in development for use in the treatment of NSCLC. In regards to the IGF-1R monoclonal antibodies, there has been a worrisome safety and efficacy signal from the phase III trial of the combination of figitumumab, carboplatin, and paclitaxel in patients with squamous cell cancer of the lung.[10] Nevertheless, there have been no new safety signals to date from the other molecules in this class.

The potential role of IGFR tyrosine kinase inhibitors remains to be defined as this class of compound is in an earlier stage of development and there is little clinical data regarding toxicity or efficacy. Going forward, development of compounds targeting the IGF pathway is likely to be in combination with other agents, either with cytotoxic chemotherapy or rational combinations with other biologic therapies. Improvements in our understanding of molecular markers and the role of the IGFR signaling pathway in different tumor histologies will also help us to best use this class of compounds toward improving outcomes for patients.

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